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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/296,264	04/22/99	WRIGHT J	032396-043

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EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	8

DATE MAILED: 09/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
09/296,264	Wright et al.	
Examiner	Group Art Unit	
Schmidt	1635	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-16 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-5, 8, 13 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 8, 13 and 16 are indefinite for the language "about 20... nucleotides" since the size of SEQ ID Nos. 1-30 is 20 bases and therefore the claimed composition can not be smaller than 20 nucleotides.

Claims 1-5, 8, 13 and 16 are indefinite for the language "as set forth in Table 1" since this limitation is redundant to the identification of the claimed composition by sequence identifiers.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 5-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the growth of neuropilin in cells in culture and via injection of specific neuropilin antisense sequences to tumor cells in mice, does not reasonably provide enablement for inhibition of any neuropilin gene in any species of whole organism for the therapeutic effects claimed by any antisense having an unspecified length and sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 5 is drawn to a pharmaceutical composition which implies whole organism application of the claimed composition. Thus the claim falls within the instant rejection for lack of enablement of the claimed composition in any whole organism for the reasons below involving administration of a nucleic acid construct such as antisense to a whole organism. Amendment of the claim to delete the word 'pharmaceutical' in the preamble and further description of an 'effective amount' of the claimed antisense oligonucleotides (i.e. effective for what?) would place claim 5 in condition for allowance.

Claims 6-16 are drawn to methods of inhibiting the growth of a mammalian tumor in a mammal, inhibiting the metastasis of a mammalian tumor and inhibiting neovascularization in a mammal by administering an "effective amount" of an antisense oligonucleotide from "about 3 to about 100 nucleotides" comprising a sequence complementary to a mammalian neuropilin mRNA under conditions such that the growth of the tumor is inhibited, such that metastasis of the tumor

is inhibited or so that neovascularization is inhibited. Dependent claims specificity that the oligonucleotide comprises one of SEQ ID NOS. 1-30.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained.

The specification as filed teaches administration of specific antisense to inhibit neuropilin/VEGF165R in cells in culture and in mice. The scope of the invention drawn to any antisense having 'about 3 to about 100 nucleotides' is not enabled as broadly claimed because of the unpredictability in the art for the design of functional antisense as argued above. The claims are enabled for the specific antisense sequences taught by way of example to function in cells for decreased target gene expression.

The specification as filed further teaches by way of example antisense administration to cancerous cells in culture (for example, Figure 1) and injection of SEQ ID NO:2 into HT-29 tumor cells in CD-1 nude mice. The specification teaches injection of various antisense known in

the art (see example 4 and figure 4) to C8161 human melanoma cells injected in CD-1 athymic female nude mice.

It is known in the art that, *in vitro* results with one antisense molecule are not predictive of any *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) *In vivo*, however, antisense have numerous problems with non-specific binding and toxicity (Branch). Although it is known in the art that certain mouse disease models accurately demonstrate an expectation of success of drug delivery in humans, the field of gene therapy, including delivery of nucleic acid constructs such as antisense to whole organisms is not predictable based on murine data alone. Crystal et al. teach that 'humans are not simply large mice' and that tumor regression and toxicity in humans is not predictable based on experimental animal data. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules in any whole organism and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense

molecules in any whole organism as broadly claimed. Specifically the specification does not teach (1) stability of any neuropilin antisense molecule *in vivo*, (2)effective delivery to a whole organism and specificity to the target tissues other than via injection to certain murine examples, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects broadly claimed . These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

5. SEQ ID NOS 1-30 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
September 22, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER